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A Prospective Epidemiological Survey of the Natural History of Chronic Critical Leg Ischaemia

The i.c.a.i. Group (gruppo di studio dell'ischemia cronica critica degli arti inferiori)*

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Objective: *To draw a picture of the different practices adopted for the diagnosis, specific treatment and general care of critical leg ischaemia (CLI) in the light of the recommendations of the recent Consensus Document.*
Design: *Prospective observational study.*
Setting: *A representative sample of vascular and general surgery, angiology, general medicine departments of the Italian National Health Service.*
Subjects: *Patients with leg ischaemia considered as chronic and critical according to the definition and diagnostic criteria adopted in each centre.*
Chief outcome measures: *Epidemiological profile of the standard population; prevalence of definition criteria and of diagnostic and therapeutic procedures; short and medium-term clinical outcome as well as of the general vascular morbidity and mortality.*
Main results: *Over a 3 month period, 574 patients were recruited in 69 centres mainly on the basis of clinical findings of CLI (rest pain and/or trophic lesions). They had an adequate diagnostic assessment of their vascular lesions and a high cardiovascular risk in terms of prior morbidity and presence of risk factors. Over half of the patients underwent revascularisation and three quarters were given pharmacological treatments. At the end of the observation period, 50 patients had died (8.7%), three had had a myocardial infarction (0.5%), six a stroke (1.0%), 70 a major amputation (12.2%) and 103 had persistent CLI (17.9%).*
Conclusions: *This survey confirms the dramatic prognosis of patients with CLI and provides an appropriate background and setting to conduct experimental clinical studies in this field.*

Key Words: Epidemiology; Peripheral vascular disease; Critical leg ischaemia.

Introduction

Chronic critical leg ischaemia (CLI) is still an "orphan" disease with respect to the availability of reliable epidemiological data and standardised clinical approaches. The reasons may be sought both in the complexity of the disease itself and in the number of pathogenetic mechanisms involved, as well as in the uncertainties existing with respect to the effectiveness of the currently available therapeutic interventions.

Recently CLI has been awarded some attention due to the publication of two Consensus Documents by the European Working Group on Chronic Critical Leg Ischaemia.[1,2] It seemed useful to address the many unsettled issues of CLI in order to draw a reliable profile of the different procedures and interventions adopted in the diagnosis and in the treatment of CLI, and to obtain quantitative evidence on the practicability of the measures recommended by the Consensus Documents. This epidemiological approach was also undertaken with a view to identifying sizeable populations of patients as potential candidates for controlled clinical trials of various interventions.

Methods

About 100 centres involved in the care of CLI in Italy (vascular and general surgery as well as angiology and medical departments) were identified and invited to a seminar to discuss the main statements of the

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most recent Consensus Document.[2] An epidemiological survey was proposed in order to describe the characteristics and clinical outcome of patients with CLI and to evaluate the consistency of the diagnostic and therapeutic practices with those recommended by the European Consensus.

For each patient admitted to each centre with a diagnosis of documented leg ischaemia considered as "chronic and critical" according to local criteria, a monitor recorded the following information: demographic data, previous clinical history including cardiovascular events, time of onset of peripheral disease and presence of major cardiovascular risk factors; characteristics of the symptoms and signs qualifying the ischaemia as chronic and critical; diagnostic procedures undertaken; number, side(s) and level(s) of vascular obstruction(s); invasive procedures and/or pharmacological treatments; major amputations and relevant clinical events including death.

All patients were admitted sequentially and were recruited over two predefined 45 day periods in different seasons (May–June and October–November). For each patient enrolled a follow-up visit was planned 3 months after hospital discharge (regardless of the length of hospitalisation) to document survival or report the date and cause of death and to record major amputations, persistence of CLI, and any treatment undertaken following discharge from the index admission. For patients lost to follow-up mortality data have been obtained through census offices.

Auditing was provided by a central secretariat, assessing the consistency and completeness of the data reported for each patient. Standard descriptive statistics were used to report study results. Since obviously contraindicated by the descriptive nature of the study, none of the apparent differences among subgroups of the study population have been formally tested for statistical significance.

Results

Recruitment and follow-up

Sixty-nine centres — 49 vascular surgery (71.0%) and 20 angiology (29.0%) departments — participated. Five hundred and seventy four patients were classified as having a critical ischaemia of the lower limbs. Each centre recruited an average of 8.4 patients (range 1–36). Surgical centres recruited 75.3% of the overall study population (432 patients).

The average observation period, including the hospital phase was 26.2 ± 19.7 days (median 20.5 days) and the 3-month follow-up, was 102.9 ± 45.5 days (median 109 days). Complete follow-up information was obtained on 507 patients (88.3%). The group of sixty-seven patients (11.7%) lost to follow-up did not substantially differ from the overall study population with respect to age, prevalence of diabetes, incidence of previous and in-hospital cardiovascular events and amputations, and unsuitability for surgery. Some informations were nonetheless available for all but six patients of this group: 60 out of 61 were alive at 3 months after discharge, eight had suffered from an in-hospital event (seven amputations and one myocardial infarction) and one patient died within 3 months of discharge.

Baseline characteristics

The mean age was 70.8 (± 9.7 S.D.; median 70.7; range 34–91) (Table 1). Three quarters of the subjects (431/574, 75.1%) were male. The majority (496, 86.4%) had a history of intermittent claudication diagnosed over the previous 2 years in two-thirds of the patients (322, 64.9%) and in the previous year in over one-third (185, 37.3%). One third of the patients had already undergone invasive interventions: 9.4% amputation

Table 1. Baseline characteristics of the study population overall and according to admission to surgical or medical wards

	Total n=574	Surgical wards n=432	Medical wards n=142
Age: mean ± S.D.	70.8±9.7	70.3±9.6	72.3±10.0
median	70.7	70.2	72.7
		n (%)	
Sex (male)	431 (75.1)	330 (76.4)	101 (71.1)
Previous cardiovascular morbidity:			
Myocardial infarction	105 (18.3)	68 (15.7)	37 (26.1)
Stroke	58 (10.1)	39 (9.0)	19 (13.4)
Claudicatio intermittens	496 (86.4)	379 (87.7)	117 (82.4)
Previous surgical interventions:			
Reconstructive surgery	109 (19.0)	99 (22.9)	10 (7.0)
PTA	21 (3.7)	15 (3.5)	6 (4.2)
Amputation	54 (9.4)	39 (9.0)	15 (10.6)
– major	32 (5.6)	25 (5.8)	7 (4.9)
– minor	22 (3.8)	14 (3.2)	8 (5.6)
Risk factors:			
Arterial hypertension	328 (57.1)	245 (56.7)	83 (58.5)
Diabetes mellitus	170 (29.6)	124 (28.7)	46 (32.4)
Hypercholesterolemia	85 (14.8)	73 (16.9)	12 (8.5)
Obesity	35 (6.1)	28 (6.5)	7 (4.9)
Smoking			
– past	272 (47.4)	211 (48.8)	61 (43.0)
– current	141 (24.6)	108 (25.0)	33 (23.2)

Table 2. Clinical picture of CLI at recruitment

	Total n=554*	Surgical wards n=417	Medical wards n=137
Pain ≥ 15 days	485 (87.5)	368 (88.2)	117 (85.4)
Use of analgesics ≥ 15 days	343 (61.9)	262 (62.8)	81 (59.1)
Ulcers or gangrene	352 (63.5)	269 (64.5)	83 (60.6)
Others	129 (23.3)	85 (20.4)	44 (32.1)

n (%).
*20 patients with missing data.

Table 3. Diagnostic procedures performed during hospital stay

	Total n=574	Surgical wards n=432	Medical wards n=142
Doppler sonography*	519 (90.4)	395 (91.4)	124 (87.3)
Angiography	443 (77.2)	374 (86.6)	69 (48.6)
Doppler and/or angiography	561 (97.7)	425 (98.4)	136 (95.8)
Others:			
Eco Doppler†	196 (34.1)	128 (29.6)	68 (47.9)
Pletismography	73 (12.7)	28 (6.5)	45 (31.7)
Capillaroscopy	19 (3.3)	3 (0.7)	16 (11.3)
tc p02	56 (9.8)	35 (8.1)	21 (14.8)
Laser Doppler	37 (6.4)	22 (5.1)	15 (10.6)

n (%).
*M-mode, continuous wave Doppler.
†Duplex or color Doppler.

(5.6% major, 3.8% minor); 19.0% reconstructive surgery (more common among patients admitted to surgical departments) and 3.7% percutaneous transluminal angioplasty (PTA).

A history of myocardial infarction was reported for 105 patients (18.3%; 15.7% of those admitted to surgical departments and 26.1% of those admitted to medical departments), while 58 patients had had a stroke (10.1%). Arterial hypertension (defined as systolic blood pressure ≥ 160mmHg and/or diastolic blood pressure ≥ 95 mmHg, or presence of antihypertensive treatment), was the most common (57.1%) cardiovascular risk factor. Almost one third of the patients (29.8%) were diabetic (fasting serum glucose levels ≥7.8 mmol/l (140 mg/dl) or ongoing treatment with insulin or oral hypoglycaemic agents); a quarter (24.7%) were current smokers, and half of the patients (47.6%) were ex-smokers. Hypercholesterolaemia (serum total cholesterol levels ≥6.4 mmol/l (250 mg/dl) or ongoing cholesterol-lowering treatment) was present in 14.8% of the patients, particularly among those admitted to surgical departments (16.9% *vs.* 8.5% in medical wards). Seven percent of the patients were obese (body mass index–[(body weight in Kg)/(height in m)^2] = ≥ 30).

Clinical picture of CLI

The clinical picture of CLI at the time of recruitment is reported in Table 2. Recurrent rest pain lasting for at least 15 days was the most common symptom (87.5%) and analgesic drugs had been prescribed to 61.9% of the patients. Trophic lesions were present in 63.5% of subjects and in 315 patients (56.9%) the trophic lesions were associated with recurrent rest pain. Only a minority of patients (5.8%) were considered "critical" even though they did not present trophic lesions or recurrent rest pain lasting for at least 15 days. A number of other factors (such as low ankle systolic pressure, or low ankle brachial pressure index) were deemed to indicate the presence of a critical condition in patients with no ulcer and a shorter history of rest pain.

Ankle or toe systolic pressures were measured in 341 (59.4%) patients. A systolic pressure < 50mmHg at the ankle and/or < 30mmHg at the toe was reported in 182 subjects (53.4% of those in whom it was measured). The resting ankle brachial pressure index (ABPI) was available for 243 patients. ABPI was < 1 in all but one of these subjects; < 0.7 in 230 (94.6%); < 0.5 in 201 (82.7%). Among non-diabetic patients (173, 71.2%) ABPI was < 0.7 in 161 (93.1%) and < 0.5 in 146 (84.4%). Among diabetics (70, 28.8%) it was < 0.7 in 68 (97.1%) and < 0.5 in 55 (78.6%).

Doppler waveform analysis was the most widely used diagnostic procedure (90.4% of the patients) (Table 3). Over three-quarters of the patients underwent angiography, more often in surgical (86.6%) than in medical (48.6%) departments. Almost all patients (97.7%) underwent one or both diagnostic procedures. More sophisticated diagnostic tests, particularly those evaluating the peripheral microcirculation, were less commonly used, and mostly in medical departments.

Only four patients (0.7% of the study population) did not suffer from a vascular obstruction. Single lesions were found in 85 patients (14.8%), 57 of whom had a proximal obstruction (i.e. above the knee). Of the patients presenting more than one lesion, 392 (68.3%) had multiple obstructions: 137 (23.9%) in the thigh, 176 (30.7%) in the leg, and 79 (13.8%) in both segments. In 181 patients (31.5%) both lower limbs were affected: 100 (17.4%) at thigh level, 26 (4.5%) at leg level, and 25 (4.4%) at both segments. One half of these patients (90) had multiple obstructions in both limbs.

Treatment

Interventional procedures were performed during the hospital stay in over half (330, 57.5%) of the patients (Table 4). Reconstructive surgery was the most common treatment: 34.0% and 7.7% of the patients underwent bypass grafting and thromboendoarterectomy respectively. These interventions were almost exclusively performed in patients admitted to surgical centres. Percutaneous transluminal angioplasty was less commonly undertaken (7.1% of the patients); surgical sympathectomy was used in 9.5% of the cases, epidural spinal electrostimulation in 3.8% and minor amputations in 5.2%. Invasive procedures were carried out on 68.5% of patients admitted to surgical departments (296/432 patients) and on 23.9% of those admitted to medical departments (34/142).

The wider adoption of surgery among those admitted to surgical departments is largely explained by the referral of patients to either surgical or medical centres, according to their clinical picture and suitability for intervention. For 38 surgical patients (8.8%) revascularisation procedures (bypass grafting, thromboendoarterectomy, PTA) were considered unsuitable on the basis of their general clinical conditions, 62 (14.4%) of peripheral circulation conditions, and 16 (3.7%) for both reasons. For 38 medical patients (26.8%) revascularisation procedures were considered unsuitable on the grounds of their general clinical conditions, 33 (23.2%) of peripheral circulation conditions and 6 (4.2%) for both reasons. Immediate revascularisation was deemed unnecessary in 68 (15.7%) and 34 (23.9%) surgical and medical patients respectively.

Three-quarters of the patients (429, 74.7%) (Table 5) received a pharmacological treatment; drug treatments were used alone or with revascularisation procedures. Over half were treated with vasoactive drugs; also drugs interfering with the haemostatic system (heparin, antiplatelet agents, defibrotide) were widely used. Prostanoids were administered to 5.2%.

Table 4. Inpatient interventional treatments

	Total n=574	Surgical wards n=432	Medical wards n=142
Bypass	195 (34.0)	185 (42.8)	10 (7.0)
Thromboendoarterectomy	44 (7.7)	44 (10.2)	0 (0.0)
PTA	41 (7.1)	30 (6.9)	11 (7.8)
Sympathectomy	55 (9.6)	45 (10.4)	10 (7.0)
Epidural spinal electrostimulation	22 (3.8)	18 (4.2)	4 (2.8)
Minor amputation	30 (5.2)	25 (5.8)	5 (3.5)

n (%).

Table 5. Inpatient pharmacological treatments

	Total n=574	Surgical wards n=432	Medical wards n=142
Vasoactive drugs	296 (51.6)	187 (43.3)	109 (76.8)
Heparin and heparinoids	215 (37.5)	149 (34.5)	66 (46.5)
Antiplatelet agents	120 (20.9)	76 (17.6)	44 (31.0)
Defibrotide	60 (10.5)	44 (10.2)	16 (11.3)
Fibrinolytic agents	31 (5.4)	27 (6.3)	4 (2.8)
Prostanoids	30 (5.2)	22 (5.1)	8 (5.6)
Haemodiluting agents	22 (3.8)	19 (4.4)	3 (2.1)
Others	63 (11.0)	41 (9.5)	22 (15.5)

n (%).

Vasoactive drugs, antiplatelet agents and heparinoids were more frequently used in medical departments; in contrast, thrombolysis was mainly performed by surgeons. Other procedures, such as peridural anaesthesia, lumbar chemical sympathectomy, isovolemic haemodilution, hyperbaric oxygen therapy were used in a minority.

Outcome

Fifty patients (8.7%) died during the observation period (Table 6). The deaths were mainly due to vascular causes (29 *vs.* 9 non-vascular deaths; in 11 cases the cause of death was not reported). About $\frac{1}{2}$ of the deaths (26; 53.1%) occurred during the hospital phase, 6 of which (12.2%) were within the first week of hospitalisation. Acute myocardial infarctions and strokes were less frequent: (2.3 and 3.1%, respectively); two-thirds (20 out of 31) were fatal events or occurred in patients who subsequently died.

During the whole study period 84 (14.6%) patients underwent major amputations (Table 6). Fourteen amputees subsequently died. Most of the amputations (53, 62.4%) were performed during the hospital phase, 14 (16.7%) within the first week of admission. Although the incidence of major amputations during the index hospitalisation was higher in surgical wards, over the entire observation period the highest incidence was among patients admitted to medical wards. Rest pain and/or ulcers or gangrene were still present in 103 (17.9%) patients at follow-up. In addition, 11 amputees developed pain and/or ulcer of the other leg. Therefore, over two-thirds of the survivors not undergoing amputation had recovered from their critical status.

The overall evaluation of clinical outcomes is presented in Table 7. It is noteworthy that only 286 patients (49.8%) were alive, did not suffer from any major event and had recovered from CLI 3 months

Table 6. Major clinical events occuring during hospitalisation and after discharge

	In hospital			After Discharge			Total		
	Total (*n*=574)	Surgical wards (*n*=432)	Medical wards (*n*=142)	Total (*n*=542)*	Surgical wards (*n*=382)	Medical wards (*n*=125)	Total (*n*=574)	Surgical wards (*n*=432)	Medical wards (*n*=142)
Death	26 (4.5)	18 (4.2)	8 (5.6)	24 (4.5)	18 (4.7)	6 (4.8)	50 (8.7)	36 (8.3)	14 (9.9)
Major amputation	53 (9.2)	38 (8.8)	15 (10.6)	32 (6.3)	20 (5.2)	12 (9.6)	85 (14.8)	58 (13.4)	27 (19.0)
Myocardial infarction	6 (1.0)	5 (1.2)	1 (0.7)	7 (1.4)	6 (1.6)	1 (0.8)	13 (2.3)	11 (1.9)	2 (1.4)
Stroke	8 (1.4)	6 (1.4)	2 (1.4)	10 (2.0)	8 (2.1)	2 (1.6)	18 (3.1)	14 (3.2)	4 (2.8)

n (%).
*Includes all patients but those who died during the in-hospital phase (*n*=26) and those (*n*=6) for whom no information was available at follow-up.
Patients who suffered multiple events are counted more than once.
In three patients the same event occured twice (two amputations, two myocardial infarctions, two strokes respectively) during the study period.

after discharge. As many as 177 survivors (30.8%) became amputees and/or had persistent critical ischaemia of the lower limbs. Moreover, though alive at 3 months, nine patients (1.6%) had suffered from a myocardial infarction or a stroke. In summary out of 574 CLI patients 3 months after discharge, 50 subjects (8.7%) had died and 181 (31.5%) had experienced at least one major vascular event (myocardial infarction or stroke) and/or had undergone major amputation and/or were still suffering from critical ischaemia (Table 7).

Discussion

This is the first large epidemiological study conducted since the publication of the last European Consensus Document on CLI[2] and the data presented provides an updated profile of CLI to compare with that suggested by the Consensus. According to the study aims, the results are discussed under two main headings: (a) the clinical profile of the disease and (b) the quality and setting-dependent variability of diagnostic criteria and treatment.

Table 7. Clinical outcome 3 months after discharge

	Total (*n*=574)	Surgical wards (*n*=432)	Medical wards (*n*=142)
Dead	50 (8.7)	36 (8.3)	14 (9.9)
Alive			
Without major events or persistent CLI	286 (49.8)	225 (52.1)	61 (43.0)
With persistent CLI without other events	103 (17.9)	75 (17.4)	28 (19.7)
With major amputation regardless of other events	70 (12.2)	47 (10.9)	23 (16.2)
With myocardial infarction or stroke, regardless of persistent CLI/major amputation*	9 (1.6)	6 (1.4)	3 (2.1)

n (%).
*Four patients suffered only from myocardial infarction (*n*=3) or stroke (*n*=1). Four patients with persistent CLI and an amputee had a stroke.

Clinical profile

The clinical profile outlined indeed confirms the severity of the condition, both in terms of mortality and of serious complications in the short term. At the end of the 3 month follow-up period, 40.2% had either died or suffered from a myocardial infarction, a stroke, a major amputation and/or persistent CLI. The only positive note comes from survivors not undergoing amputation, since their odds of recovering from CLI, i.e. of reaching ulcer healing and pain relief, are 2 in 3.

The more favourable outcome of patients admitted to surgical department as compared with those of medical wards is likely to be due to their different prognosis at the time of admission rather than to the general care and specific interventions provided in the two settings. The slight difference in mortality between surgical and medical wards is attributable to the preferential admission to medical departments of patients unsuitable for surgery on the grounds of their poor general conditions, regardless of the peripheral vascular situation (31.0% of the medical patients *vs.* 12.5% of the surgical cases). The striking difference in the amputation rate may be due to similar reasons: patients unsuitable for reconstructive surgery are more likely to be admitted to medical departments for

alternative therapeutic strategies until amputation becomes unavoidable. Indeed, the only excess of amputation reported in surgical wards compared to the medical ones (14 *vs.* none) concerns the operations performed within one week from admission, i.e. those which could not be delayed.

Quality of care

Patients with CLI were identified on the basis of their clinical picture. Indeed, among the criteria suggested by both the European Consensus[2] and the IVS Working Party,[3] those more closely adhering to the clinicians' concept of a critical peripheral situation seem to be the clinical ones (e.g. presence of rest pain for at least 2 weeks regardless of concomitant use of analgesics and/or trophic lesions). These criteria apply to almost all the patients recruited in this study. In contrast, the simultaneous presence of low peripheral systolic pressure, as suggested by the Consensus recommendations, would have restricted the diagnosis of CLI to less than 20% of the patients, who nonetheless from a clinical point of view were deemed "critical". This parameter is in fact neither widely measured nor necessarily altered in patients with CLI: indeed, the systolic pressure at the ankle or toe was only measured in about half of the patients, and only $\frac{1}{2}$ of these had values below the standard threshold indicated by the Consensus. The inclusion among diagnostic criteria of the concomitant use of analgesics, the presence or absence of which does not necessarily define the symptoms' nature and degree, would have restricted the diagnosis of CLI to 80% of the study population. Though recognised as a predictor of total mortality (not only of vascular deaths)[4,5] and since long recommended as the simplest measure to detect arterial disease of the lower limbs,[6] ABPI is considered less relevant as a diagnostic criterion than absolute ankle pressure in patients with CLI[2] possibly being more useful in the assessment of early stages of peripheral artery disease. In this study ABPI was evaluated in about $\frac{1}{2}$ of the cases, and four-fifths of the patients had values of 0.5 or less. The assessment of the criteria adopted in each centre to classify limbs as "critical" aimed at establishing a standard reference shared by the members of the collaborative group, to be used in epidemiological and clinical studies. The choice of a simple clinical definition of CLI may overcome a limitation of those currently recommended because although they may be useful for identifying subgroups at higher risk of amputation or death,[3] they are of doubtful clinical usefulness. Indeed, patients with different manifestations of the disease ultimately share the same clinical outcome, and no treatment has been proved effective in improving the prognosis of any subgroup at risk. On the other hand, in contrast with the Consensus suggestion, simple definition criteria are more adequate for clinical trials addressing general questions concerning the population of patients with CLI. This approach would ensure a wider applicability of the trials results, whilst allowing the identification of particular subgroups. Arteriography, recommended by the European Consensus[2] among the diagnostic procedures for all patients with CLI, was performed in three-quarters of patients, more commonly in surgical than in medical centres. However, almost all patients underwent either arteriography or Doppler analysis, which documented an arterial obstruction or stenosis in all but four patients.

Over half of the patients underwent invasive interventions, mostly bypass grafting procedures. Thromboendoarterectomy and PTA were rarely performed. The scanty involvement of interventional radiologists, and the lack of wide expertise and of appropriate facilities may have limited the use of less invasive procedures such as angioplasty. Although wider use of endovascular techniques is encouraged in agreement with the general trend favouring non-invasive intervention procedures,[7,8] the Consensus recommendation to attempt percutaneous catheter procedures whenever possible[2] as a first choice must be regarded in the light of reports questioning the effectiveness of angioplasty with respect to avoiding amputation or reconstructive intervention.[9] Patients admitted to surgical departments underwent intervention more often, as a result of their clinical condition and their suitability for surgery. Indeed, only a quarter (116, 26.9%) of surgical patients as compared with over half (77, 54.2%) of the medical ones were considered unsuitable for surgery. On the other hand, intervention was considered unnecessary in 68 (15.7%) and in 34 (23.9%) surgical and medical patients respectively.

The pharmacological treatments undertaken in three-quarters of the patients involved several classes of drugs and reflects the existing uncertainties on the efficacy of available medications and of the impact of market pressures. This is a situation clearly requiring further clinical research, as already stated in the Consensus Document.[2] Over half of the patients were treated with vasoactive drugs, regardless of the widespread doubts on their efficacy.[10] Heparin and heparinoids were commonly used, though not as commonly as recommended by the Consensus regarding thromboprophylaxis given the

high frequency of surgical interventions. Although the current use of heparin in surgical patients may represent an adequate practice (as documented by an ad hoc study recently performed in Italy[11]), it is noteworthy that this treatment was more common in medical than in surgical centres. Antiplatelet agents were only given to one-fifth of patients. This may indicate underprescription in the light of the high cardiovascular risk of these patients and of the general[12,13] and specific[14] usefulness of these drugs. Thrombolysis for CLI was rarely attempted, in accordance with the recommendations of the European Consensus, which has increasingly limited the indications for this pharmacological approach.[1,2] Defibrotide was widely used despite the lack of definite proofs of efficacy.[15] Prostanoids, which had not been introduced onto the Italian market when the study was performed, were only used in a small fraction of the study population, compared to the recommendations of the Consensus,[2] based on their promising pharmacological properties[16] and preliminary clinical findings of efficacy.[17]

Besides drawing an accurate picture of the characteristics of patients with CLI and of the current clinical procedures adopted, this study documents the interest of clinicians involved in the management of these patients in the epidemiology of the condition. Over 100 centres in Italy were willing to take part in a collaborative group and 69 actually contributed to the preliminary epidemiological survey. The importance of the i.c.a.i. study is also related to the demonstration of the feasibility of randomised clinical trials in populations of CLI patients large enough to allow the assessment of effectiveness of interventions on hard endpoints such as mortality and major clinical events. A collaborative clinical trial conducted by the i.c.a.i. group aiming to recruit 2000 patients is currently under way.

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Appendix:

The i.c.a.i. Group was represented by:

Participating Centres: **Belgrano E.A.** and **Nardella L.**, Vascular Surgery, Santa Croce Hospital, Cuneo; **Ponzio F.** and **Nessi F.**, Vascular Surgery, Molinette Hospital, Torino; **Guala A.** and **Mazzucchetti S.**, Angiology and Geriatrics, Infermi Hospital, Biella; **Graziano L.** and **Urban I.**, General Surgery, SS. Trinità Hospital, Varallo Sesia; **Palombo D.** and **Brustia P.**, Vascular Surgery and Angiology, Regionale Hospital, Aosta; **Calzoni D., Bellone M.** and **Altieri M.**, General Surgery, S. Carlo Hospital, Milano; **Agus G.B., De Angelis R.** and **Marrocu R.**, Vascular Surgery, Santa Rita Clinic, Milano; **Grossi A.** and **Frigerio D.**, General Surgery, San Raffaele Hospital, Milano; **Biasi G.M.** and **Piglionica M.R.**, Vascular Surgery, Bassini Hospital, Milan; **Agrifoglio G., Costantini A., Della Vedova MR.** and **Miglierina L.**, Vascular Surgery and Angiology, Istituti Clinici di Perfezionamento, Milano; **Lavorato F., Emanuelli G., Rossi R.** and **Flandoli C.**, General Surgery, S. Gerardo dei Tintori Hospital, Monza; **Ponti G.B.** and **Berra S.**, General Medicine, Rho Hospital, Rho; **Losapio G.M.** and **Ambrosi R.**, Vascular Surgery, Ospedali Riuniti, Bergamo; **Inzoli M.R., Lombardi G., Tarantola P.** and **Zocca N.**, Geriatric and Rehabilitation Unit, S. Orsola Hospital, Brescia; **Sforza M.** and **Russo R.**, General Surgery, Lecco Hospital, Lecco; **Tenchini P.** and **Bruni T.**, General Surgery I, Carlo Poma Hospital, Mantova; **Fontanili M.** and **Guidetti D.**, General Surgery II, Carlo Poma Hospital, Mantova; **Odero A.** and **Salvini M.**, Vascular Surgery, San Matteo Hospital, Pavia; **Pedeferri G.** and **Bordoni M.C.**, Vascular Surgery, Bormio and Sondalo Hospital, Sondalo; **Visconti W.** and **Vedovato F.**, Vascular Surgery, G.B. Giustinian Hospital, Venizia; **Bittolo Bon G.** and **Maffei L.**, General Medicine, Civile Hospital, Venizia; **Marcon G.** and **Dell'Olivo I.**, General Medicine, Angiology and General Surgery, Mirano Hospital, Mirano; **Gracco L.** and **Petralia G.**, General Surgery, Umberto I Hospital, Mestre; **Cordiano C.** and **Dorucci V.**, General Surgery, Borgo Trento Hospital, Verona; **Pagnan A.** and **Visona' A.**, Internal Medicine, Castelfranco V.to; **Tonietto G.** and **Agresta F.**, General Surgery, Civile Hospital, Vittorio V.to; **Favretti F.** and **Burigo E.**, General Surgery, Presidio Hospital, Belluno; **Giansante C.** and **Fiotti N.**, General Medicine, Cattinara Hospital, Trieste; **Pamich G.** and **Santirocco C.**, Vascular Surgery, Civile Hospital, Gorizia; **Mozzon L.** and **Gonano N.**, Vascular Surgery, S. Maria della Misericordia Hospital, Udine; **Petrilli G.L., Puzzo A.** and **Baldinog G.**, Vascular Surgery, Galliera Hospital, Genova; **Podestà A., Guastini A.** and **Traversaro A.**, General

Surgery, Lavagna Hospital, Lavagna; **Zinicola N.** and **Baglietto F.**, Vascular Surgery, Santa Corona Hospital, Pietra Ligure; **Borgatti E., Filippini M.** and **Ferrari F.**, Angiology, Malpighi Hospital, Bologna; Ridolfi, Angiology and General Medicine, Maggiore Hospital, Bologna; **Coppi G.** and **Camparini S.**, Vascular Surgery, San Agostino Hospital, Modena; **Tuscano G.** and **Lonardi R.**, Vascular Surgery, Policlinico Modena; **Botta G.C., Banchini E.** and **Pavarini E.**, General Surgery, Maggiore Hospital, Parma; **Delmonte E.** and **Bucherini E.**, Geriatrics, Per gli Infermi Hospital, Faenza; **Moratti A.** and **Ieran M.**, general Medicine and Angiology, S. Maria Nuova Hospital, Reggio Emilia; **Bertini D.** and **Pratesi C.**, Vascular Surgery, Careggi Hospital, Firenze; **Corsi C., Pollastri M.** and **Marrapodi E.**, Angiology, Santa Chiara Clinic, Firenze; **Vanni D.** and **Ralli L.**, Internal Medicine, Centrale Hospital, Arezzo; **Cecchi M.**, Vascular Surgery, Centrale Hospital, Arezzo; **Bigalli A.** and **Del Carratore G.**, Cardiovascular Medicine, Santa Chiara Hospital, Pisa; **Mosca F.** and **Vatteroni F.**, Vascular Surgery, Cisanello Hospital, Pisa; **Setacci C.**, Vascular Surgery, Le Scotte Hospital, Siena; **Cao P.** and **Verzini F.**, Vascular Surgery, Monteluce Hospital, Perugia; **Mannarino E., Pasqualini L.** and **Fedeli F.**, General Medicine and Angiology, Monteluce Hospital, Perugia; **Alo' F.** and **Ioannidis G.**, Vascular Surgery, Torrette Hospital, Ancona; **Spartera C.** and **Marino G.**, Vascular Surgery, San Salvatore Hospital, L'Aquila; **Medori M.**, General Surgery, Civile Hospital, Giulianova; **Pola P.** and **Dal Lago A.A.**, Angiology, Gemelli Hospital, Roma; **Di Giovanani V.** and **Colli R.**, Vascular Surgery, Gemelli Hospital, Roma; **Maniscalco G.**, General Medicine and Angiology, Filippo Neri Hospital, Roma; **Bartolo M.** and **Todini A.R.**, Angiology, San Camillo Hospital, Roma; **Benedetti-Valentini F.** and **Irace L.**, Vascular Surgery, Umberto I Hospital, Roma; **Fiorani P.** and **Taurino M.**, Vascular Surgery, San Eugenio Hospital, Roma; **Marcialis A.** Vascular Surgery, Policlinico, Napoli; **Valitutti P.** and **Vigliotti G.**, Vascular Surgery, San Giovanni di Dio e Ruggi d'Aragona Hospital, Salerno; **Regina G., Fullone M.** and **Rizzo S.**, Vascular Surgery, Policlinico, Bari; **Rolli F.** and **Pascali M.**, Vascular Surgery, Di Summa Hospital, Brindisi; **Lucentini L., Grilli M.** and **Correra H.**, Internal Medicine and Angiology, Sollievo della Sofferenza Clinic, San Giovanni Rotondo; **Florena M.** and **Cassina I.**, Vascular Surgery, Paolo Giaccone Hospital, Palermo; **Notarbartolo A.** and **Belvedere M.**, Internal Medicine and Geriatrics, Paolo Giaccone Hospital, Palermo; **Andreozzi G.M., Di Pino L., Martini R.** and **Signorelli S.**, Angiology, Garibaldi Hospital, Catania; **Cavallaro S.** and **Puleo R.**, Vascular Surgery, Garibaldi Hospital, Catania; **Romeo S., Cormaci O.F., Costanzo C.** and **Grasso A.**, Vascular Surgery, Garibaldi Hospital, Catania. *Scientific and Organising Secretariat*: **Avanzini F., Bedoni P., Bellone M., Bertele' V., Colombo F., Costantini A., Fellin G., Pangrazzi J., Roncaglioni M.C., Samori G., Tognoni G.** *Policy Board*: **Agrifoglio G., de Gaetano G., Garattini S., Tognoni G.**

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